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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Agrawal et al.	GROUP:	1635
SERIAL NO.:	09/777,526	EXAMINER:	TBA
DOCKET NO.:	HYZ-030CPCN3		
FILING DATE:	February 6, 2001		

TITLE METHOD OF DOWN-REGULATING GENE EXPRESSION

CERTIFICATE OF MAILING (37 C.F.R. § 1.10)

I hereby certify that this correspondence is being deposited with the United States Postal Service as "First Class Mail" Service on May 18, 2001 and is addressed to : Commissioner for Patents, Washington, D.C. 20231

By: SLK/
Sandhya L. Kalkunte

Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Pursuant to 37 C.F.R. § 1.56 and 1.97-98, Applicants hereby make record the documents listed on the attached Form PTO-1449. Copies of all the references have been cited in a prior application, U.S. Serial No. 09/587,934, from which above patent application claims priority under U.S.C. § 120. Therefore, pursuant to 37 C.F.R. § 1.98(d), no further copies of the previously cited art are enclosed.

It is also noted that the subject application, in addition to the above priority claim, also claims priority from U. S. Patent Application Serial Nos. 08/758,0050, 8/709,910 and 08/328, 520 (*now* U.S. Patent No. 5,592,721), so that disclosure and the references cited therein should also be considered.

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, Applicants understand that the Examiner will make an independent evaluation of the cited publications.

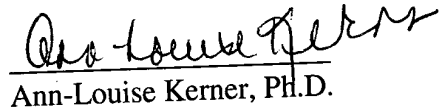
This information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits and is therefore submitted as both timely and proper and, therefore, no fees are believed to be due.

The Commissioner, however, is hereby authorized to charge and fee deficiency or credit and overpayment to Deposit Account No. 08-0219.

If there are any questions, please call the undersigned at the telephone number indicated below.

Respectfully submitted,

HALE AND DORR LLP



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Subt. For, PTO-1449

INFORMATION DISCLOSURE IN AN APPLICATION

(Use several sheets if necessary)

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Agrawal et al.	
Filing Date	**Group Art Unit**
February 6, 2001	1635

Sheet	1	OF	4

U.S. Patent Documents

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	4,309,404	1/5/1982	DeNeale et al.	424	21	
	4,309,406	1/5/1982	Guley et al.	424	21	
	4,556,552	12/3/1985	Porter et al.	424	32	
	4,704,295	11/3/1987	Porter et al.	427	3	
	5,220,007	6/15/1993	Pederson et al.	536	23.1	
	5,149,797	9/22/1992	Pederson et al.	536	23.1	
	5,220,007	12/21/1993	Cho-Chung	424	450	
	5,248,670	9/28/1993	Draper et al.	514	44	
	5,271,941	12/21/1993	Cho-Chung	424	450	
	5,403,709	10/6/1992	Agrawal et al.	435	6	
	5,442,049	8/15/1995	Anderson et al.	536	24.5	
	5,470,967	11/28/1995	Huie et al.	536	24.3	
	5,514,577	5/7/1996	Draper et al	435	238	
	5,578,716	12/1/1993	Szyf et al.	536	24.5	
	5,612,212	11/12/1993	Gewirtz	435	456	
	6,143,881	11/7/2000	Metelev et al.	536	24.5	
	5,652,355	7/29/1997	Metelev et al.	536	24.5	
	5,969,117	10/19/1999	Agrawal	536	22.1	

Foreign Patent Documents

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	94/02498	2/3/1994	WO	C07H 21	00		X
	94/15619	7/21/1994	WO	A61K 31	70		X

Other Documents (Including Author, Title, Date Pertinent Pages, Etc.)

	A1	Agrawal, Sudhir, "Functionalization of oligonucleotides with amino groups and attachment of amino specific reporter groups." *Methods Mol Biol.*, Vol. 26, pp. 93-120 (1994)
	A2	Agrawal et al., "Inhibition of human immunodeficiency virus in early infected and chronically infected cells by antisense oligodeoxynucleotides and their phosphorothioate analogues." *Proc Natl Acad Sci U S A.*, Vol. 86, No. 20, pp. 7790-4 (1989)
	A3	Agrawal, Antisense Therapeutics, (Sudhir Agrawal, ed.) , Page V (1996)

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EXAMINER: Initial if citation is considered, whether or not citation is in conformance with MPEP § 609: Draw Line through citation if not conformance and not considered. Include copy with next communication to applicant.

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INFORMATION DISCLOSURE IN AN APPLICATION

(Use several sheets if necessary)

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Filing Date	Group Art Unit
February 6, 2001	1635

Sheet 2 OF 4

	A4	Agrawal et al., "Site-specific excision from RNA by RNase H and mixed-phosphate-backbone oligodeoxynucleotides." *Proc Natl Acad Sci U S A.*, Vol. 87, No. 4, pp. 1401-5 (1990)
	B1	Agrawal et al., "Pharmacokinetics, biodistribution, and stability of oligodeoxynucleotide phosphorothioates in mice." *Proc Natl Acad Sci U S A.*, Vol. 88, No. 17, pp. 7595-9 (1991)
	B2	Agrawal et al., "Absorption, tissue distribution and in vivo stability in rats of a hybrid antisense oligonucleotide following oral administration." *Biochem Pharmacol.*, Vol. 50, No. 4, pp. 571-6 (1995)
	B3	Agrawal et al., "Antisense oligonucleotides as antiviral agents." *Trends in Biotechnol.*, Vol. 10, pp. 152-158 (1992)
	B4	Agrawal et al., "Oligodeoxynucleoside phosphoramidates and phosphorothioates as inhibitors of human immunodeficiency virus." *Proc. Natl. Acad. Sci.* (USA), Vol. 85, pp. 7079-7083 (1988)
	B5	Agrawal, S., "History of Antisense Oligonucleotides" in Antisense Therapeutics (Sudhir Agrawal ed.), Human Press, Totowa, New Jersey (1996)
	B6	Craig et al., *Exp. Opin. Ther. Patents* 7:1175-1182 (1997)
	B7	Bayever et al., "Systemic administration of a phosphorothioate oligonucleotide with a sequence complementary to p53 for acute myelogenous leukemia and myelodysplastic syndrome: initial results of a phase I trial." *Antisense Res Dev.* Vol. 3, No. 4, pp. 383-90 (1993)
	B8	Boutorine et al, *Biochimie* 76: 23-32 (1994)
	B9	Ceruzzi et al., *Nucleosides and Nucleotides* 8 (5&6): 815-8 (1989)
	B10	Egli et al. (10/8-9/98) Antisense 98, Targeting the Molecular Basis of Disease, pp. 37
	B11	Furdon et al., "RNase H cleavage of RNA hybridized to oligonucleotides containing methylphosphonate, phosphorothioate and phosphodiester bonds." *Nucleic Acids Res.*, Vol. 17, No. 22, pp. 9193-204 (1989)
	B12	Galderisi et al., "Antisense oligonucleotides as therapeutic agents." *J. Cell. Physiol.*, Vol. 181, pp. 251-57 (1999)
	B13	Hughes et al., "Radiolabeling of methylphosphonate and phosphorothioate oligonucleotides and evaluation of their transport in everted rat jejunum sacs." *Pharm Res.*, Vol. 6, pp. 817-24. (1995)
	B14	Isis Pharmaceuticals –Press Release 060500, June 5 (2000)
	B15	Isis Pharmaceuticals, Inc., *Antisense 97: Targeting the Molecular Basis of Disease,* Nature Biotechnology Conference, May 1-2 1997
	B16	International Business Communications, *IBC,'s Fourth Annual International Sysmposium on Oligonucleotides and Gene Therapy-Based Antisense Therapeutics with New Applications for Genomics,* February 6-7 1997
	B17	International Business Communications, *IBC,'s Sixth Annual International Conference on Oligo-Therapeutics, Molecular Tools and Novel Therapeutic Strategies,* May 1999

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	Applicant: Agrawal et al.	
Sheet 3 OF 4	Filing Date: February 6, 2001	Group Art Unit: 1635

	B17	Inoue et al., "Sequence-dependent hydrolysis of RNA using modified oligonucleotide splints and RNase H." *FEBS Lett.*, Vol. 215, No. 2, pp. 327-30 (1987)
	B18	Inoue et al., *FEBS Lett.*, Vol. 215, pp. 237-250 (1987)
	B19	Iversen, "In vivo studies with phosphorothioate oligonucleotides: pharmacokinetics prologue." *Anticancer Drug Des.*, Vol. 6, No. 6, pp. 531-8 (1991)
	C1	Iversen, "Pharmacokinetics of an antisense phosphorothioate oligodeoxynucleotide against rev from human immunodeficiency virus type 1 in the adult male rat following single injections and continuous infusion." *Antisense Res Dev.*, Vol. 4, No. 1, pp. 43-52 (1994)
	C2	Kawasaki et al., "Uniformly modified 2'-deoxy-2'-fluoro phosphorothioate oligonucleotides as nuclease-resistant antisense compounds with high affinity and specificity for RNA targets." *J Med Chem.*, Vol. 36, No.7, pp. 831-41 (1993)
	C3	Levin (10/8-9/98) Antisense 98, Targeting the Molecular Basis of Disease, pp. 25
	C4	Martin, P . *Helvetica Chimica Acta*, 78: 486-504 (1995)
	C5	Metelev et al, *Bioorganic & Medicinal Chemistry Letters*, 4: 2929-2934 (1994)
	C6	Milligan et al., "Current concepts in antisense drug design." *J Med Chem.*, Vol. 36, No. 14, pp. 1923-37 (1993)
	C7	Orr, (Reported By) Antisense 98: "Targeting the Molecular Basis of Disease (Part III)" Organized by Nature Biology, London, UK (1988)
	C8	Quartin et al., "Number and distribution of methylphosphonate linkages in oligodeoxynucleotides affect exo- and endonuclease sensitivity and ability to form RNase H substrates." *Nucleic Acids Res.*, Vol. 17, No. 18, pp. 7253-62 (1989)
	C9	Rapaport et al., "Antimalarial activities of oligodeoxynucleotide phosphorothioates in chloroquine-resistant Plasmodium falciparum." *Proc Natl Acad Sci U S A.*, Vol. 89, No. 18, pp. 8577-80 (1992)
	C10	Sands, "Biodistribution and metabolism of internally 3H-labeled oligonucleotides. I. Comparison of a phosphodiester and a phosphorothioate." *Mol Pharmacol.*, Vol. 45, No. 5, pp. 932-43 (1994)
	C11	Shibahara et al., "Site-directed cleavage of RNA." *Nucleic Acids Res.*, Vol. 15, No. 11, pp. 4403-15 (1987)
	C12	Shibahara et al., "Inhibition of human immunodeficiency virus (HIV-1) replication by synthetic oligo-RNA derivatives." *Nucleic Acids Res.*, Vol. 17, No. 1, pp. 239-52 (1989)
	C13	Shibahara et al., *Nucleic Acids Res.*, Vol. 15, pp. 4403-4415 (1987)
	C14	Sonveaux, "*Protecting Groups in Oligonucleotide Synthesis", in Methods in Molecular Biology* (Agrawal ed.) 26:1-71 (1994)
	C15	Stein et al., "Antisense oligonucleotides as therapeutic agents--is the bullet really magical?" *Science*, Vol. 261, No. 5124, pp. 1004-12 (1993)
	C16	Takashima et al., "Tau protein kinase I is essential for amyloid beta-protein-induced neurotoxicity." *Proc Natl Acad Sci U S A.*, Vol. 90, No. 16, pp. 7789-93 (1993)
	C17	Tidd et al., "Partial protection of oncogene, anti-sense oligodeoxynucleotides against serum nuclease degradation using terminal methylphosphonate groups." *Br J Cancer.*, Vol. 60, No. 3, pp. 343-50 (1989)

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	C18	Tortora et al., "Oral antisense that targets protein kinase A cooperates with taxol and inhibits tumor growth, angiogenesis, and growth factor production." *Clin Cancer Res.* Vol. 6, No. 6, pp. 2506-12 (2000)
	C19	Tseng et al., "Antisense oligonucleotide technology in the development of cancer therapeutics." *Cancer Gene Ther.*;Vol. 1, pp. 65-71 (1994)
	C20	Uhlmann et al., "Antisense Oligonculeotides: A New Therapeutic Principle" *Chem. Rev.* Vol. 90, pp. 543-584 (1990)
	D1	Wang et al., "Antitumor activity and pharmacokinetics of a mixed-backbone antisense oligonucleotide targeted to the RIalpha subunit of protein kinase A after oral administration." *Proc Natl Acad Sci U S A.*, Vol. 96, No. 24, pp. 13989-94 (1999)
	D2	Wickstrom, E., "Oligodeoxynucleotide stability in subcellular extracts and culture media." *J Biochem Biophys Methods.*, Vol. 13, No. 2, pp. 97-102. (1986)
	D3	Wickstrom, E., "Strategies for administering targeted therapeutic oligodeoxynucleotides." *Trends Biotechnol.*, Vol. 10, No. 8, pp. 281-7(1992)
	D4	Zamecnic, P., "History of Antisense Oligonucleotides" in Antisense Therapeutics (Sudhir Agrawal ed.), Human Press, Totowa, New Jersey (1996) pp. 1-11.
	D5	Zhao et al., *Antisense Res. and Dev.* 3: 53-66 (1993)
	D6	Zon, *Pharm.Res* 5(9): 539-49 (1988)
	D7	Zendegui et al., "In vivo stability and kinetics of absorption and disposition of 3' phosphopropyl amine oligonucleotides." *Nucleic Acids Res.*, Vol. 20, No. 2, pp. 307-14 (1992)

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